SEQ ID NO. Applicants have amended the specification to incorporate the corresponding SEQ ID numbers on page 155 as noted by the Examiner and to incorporate the correct SEQ ID numbers elsewhere in the specification.

***Status of the Claims***

Claim 124 is pending in the application. Claim 124 has been amended and new claims 132-162 are presented in order to more particularly point out and distinctly claim that which Applicants regard as the invention. Support for the amended claims can be found generally through Applicants' specification and, in addition, the chart below illustrates where exemplary support is found for specific subject matter of the newly presented claims.

| **Claim(s)** | **Specification** |
|---|---|
| 124, 139, 145 and 153 | variants: Figures 5 and 6 depicting murine and human OB polypeptides lacking glutamine at position 49;<br><br>analogs including fragments: page 22, lines 17-23, page 32, lines 10-12;<br><br>allelic variants: page 6, lines 19-20;<br><br>muteins: page 32, lines 11-13 and lines 25-26. |
| 124, 132, 139, 140, 145, 146, 153 and 154 | amino acids 22-167 and 22-166: page 10, lines 16-20 and 21-25; page 62, line 9, illustrating signal sequence cleavage site Figures 3 and 4 at arrow showing signal sequence cleavage site. |
| 144, 154 and 160 | expression control sequence: page 52, lines 9-17; page 53, lines 9-20. |

| Claim(s) | Specification |
|---|---|
| 150 | attenuated or defective DNA virus vectors: page 83, lines 21-26;<br><br>retroviral vectors: page 84, lines 7-12. |
| 151 | liposome mediated transfection: page 84, line 13 through page 85, line 2. |
| 153 | liposome mediated transfection: page 84, line 13 through page 85, line 2;<br><br>naked DNA: page 85, lines 3-10. |
| 161 and 162 | homologous recombination: page 45, lines 4-10; page 50, lines 17-25. |

***The Specification Enables the Claimed Invention***

The Examiner has rejected claim 124 under 35 U.S.C. 112, first paragraph, because the Examiner asserts that "the specification, while being enabling for the use of a gene encoding the mouse OB polypeptide as shown in SEQ ID NOs 1 or 2 for reducing the body weight of *ob/ob* mice or normal mice, does not reasonably provide enablement for using other 'allelic variants or analogs, including fragments, thereof having the same biological activity,' or enable treating animals other than mice with the mouse OB protein disclosed". The Examiner points out two

specific issues regarding enablement of the scope of claim 24, each of which will be addressed by Applicants below.

The first issue presented by the Examiner regarding enablement involves the specific amino acid sequence of the OB polypeptide claimed. More specifically, the Examiner states that "the specification fails to identify other allelic variants, analogs or fragments thereof which would have the same 'biological activity'". The Examiner further asserts that the specification fails to provide sufficient guidance as to what constitutes a variant having the properties as claimed. Applicants respectfully disagree and submit that it is unnecessary to provide working examples of all OB polypeptides that would be biologically active so long as there is a sufficient and enabling disclosure to guide the artisan in making or obtaining recited OB polypeptides and testing them for biological activity.

In fact, the specification provides examples, evidence and guidance for the preparation and testing of variants, analogs, muteins and fragments of OB polypeptides. The specification details the cloning and sequencing of mouse and human OB polypeptide encoding DNA. Sequence comparison between the amino acid sequences of human and mouse OB shows that there are a number of divergent residues. In the Example on pages 63-64, the specification further characterizes mouse and human variants in which the Gln at position 49 is deleted. The Example at pages 62-63 details modification of the mouse and human sequences to introduce an Nde site (and a variant amino acid, methionine) at the alanine at the end of the signal sequence. In addition, a deletion mutant/OB fragment is described (on page 60, lines 19-22), identified in mutant 1J mice, with amino acids 105-167 deleted. The skilled artisan is provided guidance for variants, analogs, muteins and fragments by the above detailed examples and evidence in the specification. For instance, sites for divergent residues are readily identified.

With regard to methods for preparing modifications and analogs of OB polypeptides, the applicants submit that at the priority date of the application (8-17-94) as exemplified below, technology had already been developed which enabled workers of ordinary skill in the art, using the guidance provided by the priority specification, to routinely and without undue experimentation prepare any of the OB polypeptides (or nucleic acids encoding such OB polypeptides)

encompassed by the present claims. The references discussed below represent a snapshot of what was known and available to those of ordinary skill in the art at the relevant priority date with respect to preparing modified polypeptides by methods such as site-directed mutagenesis.

In Waye, *et al, EMBO J.* **2**:1827-1829 (1983) (Exhibit A), the authors teach a method for deletion mutagenesis which was used to direct a deletion of a cloned TyrTS gene. In January 1987, Hwang *et al., Cell* **48**:129-136 (Exhibit B)analyzed the functional domains of a *Pseudomonas* exotoxin using a deletion analysis of the gene expressed in *E. coli*. In 1986, Zumstein *et al., J. Mol. Biol.* **191**:333-340 (Exhibit C) described the analysis of the structural domains and function of *E. coli* DNA Topoisomerase I using insertion and deletion mutagenesis. In DeChiara *et al., Methods in Enzymol.* **119**:403-415 (Exhibit D), the authors describe procedures for *in vitro* DNA mutagenesis of human leukocyte interferon. Other publications describing mutagenesis of cloned genes and subsequent testing of the polypeptide product encoded thereby include Doyle *et al., J. Cell Biol.* **103**:1193-1204 (1986) (Exhibit E) and others.

While some experimentation to make and test such OB polypeptides would be necessary, such experimentation would be routine and utilize well known and standard skills and would not constitute undue experimentation. With regard to the determination of what is undue experimentation, the PTO and the courts have commented that "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." MPEP § 2164.01, *citing M.I.T. v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). The test of enablement is not whether experimentation is necessary, but whether or not it is undue. *Ibid, citing In re Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976). Factors to consider in determining undue experimentation include (1) the quantity (time and expense) of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; (8) and the breadth of the claims. *Ibid, citing In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). In the present instance: (1) the quantity of experimentation, while significant, is not undue for the skilled artisan; (2) the direction or guidance provided by the specification is sufficient for the skilled artisan and appropriate for the time, even

as to the priority filing; (3) working examples are provided; (4) the nature of the invention, including, but not limited to the disclosure of DNA and protein sequence from distinct species; (5) the extent of prior art available to those skilled in the art with regard to making and testing modifications, variants, analogs or fragments was very significant at the time of the priority filing; (6) the relative skill of those in the art is substantial - the courts have determined that, in molecular biology, the level of skill in the art corresponds to that of a Ph.D. with postdoctoral experience; (7) the disclosure of sequence divergent sites and mutants in the specification enhance the predictability of making and testing modifications, variants, analogs and fragments; and (8) the breadth of the claims is commensurate with the significant skill of those in the art. In view of the foregoing, Applicants submit that given the guidance provided by the specification and the significant level of skill in the art a person of ordinary skill in the art could, without undue experimentation, prepare and test all of the OB polypeptides encompassed by the present claims.

With regard to determining those OB polypeptides, including variants, analogs or fragments, which would have biological activity, that is "capable of modulating body weight" as indicated in the present claims, one skilled in the art could test any such OB polypeptides using a functional assay for biological activity, as for instance exemplified in the specification. The specification details the ability of the OB protein to decrease body fat when purified protein is administered (as described in Examples 16 and 17). Applicants submit that demonstration of such activity in an animal is a simple, reproducible and predictable means to test biological activity. Such activity is tested simply by administering to an animal a polypeptide (or nucleic acids encoding a polypeptide) according to the present invention and measuring the weight change in that animal. Other tests are also described in the specification. For instance, an additional *in vivo* test of activity by transgenic complementation is presented on page 28 of the specification. Applicants also point to teaching in the specification, including at page 31, to further aid the skilled artisan seeking to characterize the biological activity of OB analogs through initial *in vitro* tests, e.g. specific binding to an OB antibody.

Significantly, the present invention, by its very nature, carries with it an exceedingly accurate, simple and predictive biological assay in the form of experimental observation of changes in body weight in a test subject. This result is both quantifiable and physically observable and in

Applicants assessment represents an ideal functional endpoint.

The routine nature of such investigation and biological testing is evidenced in PCT application WO 96/40912 (the 40912 Application) (attached hereto as Exhibit F) entitled "OB Protein Compositions and Method" which discloses the making, preparation and testing of recombinant murine methionyl OB protein and recombinant human methionyl OB protein. In Examples 1 and 2 of the 40912 Application, the modified murine OB polypeptide is administered to normal (non-obese) mice and weight loss is observed. The polypeptide of the 40912 Application contains two modifications : (a) an alanine at the end of the signal sequence (corresponding to position 22) is replaced by methionine - this modification corresponds to the modification detailed in the instant application on pages 62-63; and (b) in the human methionyl OB protein, amino acid 56, normally lysine, is replaced by arginine.

The second issue presented by the Examiner regarding enablement is in regard to the animal shown to have actual weight loss by the increased levels of OB protein *in vivo*. The Examiner comments that "although applicants have taught the gene sequence encoding the human polypeptide, there is no teaching that humans can be treated with this gene and cause a resulting increase in OB production and a modification (i.e. reduction) of body weight". The Examiner further asserts that it would constitute undue experimentation to practice the invention for its scope. Applicants respectfully disagree.

Applicants point out that the specification teaches and exemplifies the generation of vectors containing nucleic acid encoding OB polypeptides and the ability of purified mouse OB polypeptide to cause a modification (i.e. reduction) of body weight in mice. The application also describes the use of various vectors for use in gene therapy. Further, at page 5 of the response, the Examiner acknowledges that gene therapy utilizing a vector encoding the OB protein can cause a total correction of the obese phenotype of *ob/ob* mice. In addition, in Examples 1 and 2 of PCT application WO 96/40912 (the 40912 Application) (attached hereto as Exhibit F and discussed above) demonstrate that recombinant murine methionyl OB protein is administered to normal (non-obese) mice and weight loss is observed.

Applicants submit that it would not constitute undue experimentation to make and test OB

polypeptides for use in gene therapy methods of modifying body weight in humans. As discussed above, it has been demonstrated that both purified OB polypeptide and nucleic acids encoding OB polypeptides (by administration of vectors containing such nucleic acids) are capable of modulating body weight in normal and obese mice. In addition, modified mouse and human OB polypeptides (and nucleic acids encoding such modified OB polypeptides) are disclosed in Applicant's specification and could be generated, without undue experimentation, by one skilled in the art (as discussed above). Further, methods to test biological activity are also enabled and readily performed by one skilled in the art (as discussed above), allowing the skilled artisan to identify the population of individuals which would benefit from the administration of the OB gene (or polypeptide) to modify body weight as claimed.

In view of the foregoing remarks, Applicants submit that the Examiner's rejection under 35 U.S.C. 112, first paragraph may properly be withdrawn.

***Particularity and Distinctiveness of the Claims***

The Examiner has rejected claim 124 under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter applicant regards as the invention.

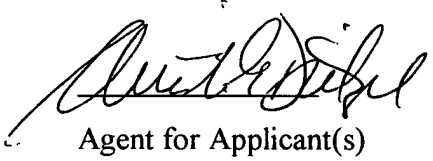
The Examiner suggests that Applicants amend claim 124 to include all of the limitations of non-elected claim 54, from which it depends. The Examiner also objects to the terms "about 145 to 167 amino acids" and "biological activity" as not clearly defined in the specification. The Examiner further objects to "administering a nucleic acid", asserting that the composition of this nucleic acid is unclear. Applicants have now amended claim 124 to include all of the limitations of non-elected claim 54 and to refer to specific SEQ ID NOs. In addition, "biological activity" is clarified to refer to OB polypeptides "capable of modulating body weight".

In view of the foregoing amendments and remarks, Applicants submit that the Examiner's rejection is obviated and should be withdrawn.

## CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,
KLAUBER & JACKSON



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